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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,193	05/11/2001	Greta Van Den Berghe	6296.204-US	5893

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NOVO NORDISK HARMACEUTICALS INC
ATTENTION: PATENT DEPARTMENT
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,193	VAN DEN BERGHE, GRETA	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-14 and 22-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 4-14 and 22-31 are pending.

Applicant's amendment and response filed January 26 and March 10, 2004 are acknowledged, and applicants' response has been fully considered. Claims 1 and 4-12 have been amended, claims 2, 3 and 15-21 have been cancelled, and new claims 22-31 have been added. Therefore, claims 1, 4-14 and 22-31 are examined.

Objection Withdrawn

2. The previous objection to the specification regarding the embedded hyperlink is withdrawn in view of applicant's amendment to the specification, and applicant's response at page 6 in the amendment filed January 26, 2004.

3. The previous objection to claims 4-5, 15, 20 and 21 is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 6 in the amendment filed January 26, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 1 and 19-21, under 35 U.S.C.112, second paragraph, regarding the claim lacking essential steps is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 8 in the amendment filed January 26, 2004.

5. The previous rejection of claims 1, 4, 5 and 9-11, under 35 U.S.C.112, second paragraph, regarding the term "and/or", "preferably insulin", or antecedent basis is withdrawn in view of

applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 8 in the amendment filed January 26, 2004.

Claim Rejections - 35 USC § 102

6. The previous rejection of claims 1, 5, 6, 12, 13 and 15 under 35 U.S.C. 102(b) as being anticipated by Rassias *et al.* (Anesthsia and Analgesia 88, 1011-1016 (May 1, 1999)), is withdrawn in view of applicant's amendment to the claim, applicant's cancellation of the claim, and applicant's response at page 9 in the amendment filed January 26, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-14 and 22-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a critically ill patient or a critically ill polyneuropathy (CIPNP) patient comprising administering an amount of insulin as a blood glucose regulator effective to maintain blood glucose level in the patient in the range of about 60 mg/dL to about 130 mg/dL, or a method of treating a CIPNP patient comprising administering an amount of insulin as a blood glucose regulator effective to reduce the incidence of CIPNP and lengthen the time free of CIPNP in patients, does not reasonably provide enablement for a method of treating a critically ill patient or a CIPNP patient comprising administering an amount of a blood glucose regulator effective to maintain blood glucose level in the patient in the range of about 60 mg/dL to about 130 mg/dL, or a method of treating a CIPNP patient comprising administering an amount of a blood glucose regulator effective to treat CIPNP, where the

structure of the blood glucose regulator is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4-14 and 22-31 encompass a method of treating a critically ill patient or a CIPNP patient by adminstering an effective amount of a blood glucose regulator to maintain the blood glucose level in the specifically defined range. The specification, however, only discloses the conclusions without sufficient data supporting the findings, which state that the critical illness in a patient or in a CIPNP patient can be treated or prevented by controlling glucose metabolism during the critical illness by applying intensive treatment with a blood glucose regulator such as insulin, active insulin derivatives or other blood glucose regulators (pages 3-4). There are no indicia that the present application enables the full scope in view of a method of treating a critically ill patient or a CIPNP patient using a blood glucose regulator as discussed in the stated rejection. The present application does not provide sufficient teachings as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding various blood glucose regulators administered and the treating conditions such as dosage of

various blood glucose regulators for the treatment of critically ill patient or a CIPNP patient, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the treatment of a critically ill patient or a CIPNP patient with insulin (Examples 1 and 2).

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Rassias *et al.*, Anesthsia and Analgesia 88, 1011-1016 (1999)) indicates insulin infusion and glucose control during surgery improves white cell function in diabetic cardiac surgery patient; and Malmberg *et al.* (JACC 26, 57-65 (1995)) disclose insulin-glucose infusion followed by a multidose insulin regimen improved long-term prognosis in diabetic patients with acute myocardial infarction. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific teachings on the treating conditions such as doses of various blood glucose regulators for treating critically ill patients or CIPNP patients and the effects of these blood glucose regulators in the treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of treating a critically ill patient or a CIPNP patient using various blood glucose regulators including insulin, insulin derivatives or insulin analogs or other glucose regulators, however, the treating conditions such as doses and the in vivo effects of various blood glucose regulators having different structures or different glucose-regulating mechanism are not adequately described in the specification, the invention is unpredictable

regarding the outcome of the treatment for patients with various critical illness using a blood glucose regulator, e.g., Rassias *et al.* teach insulin infusion and glucose control during surgery improves white cell function in diabetic cardiac surgery patient, and the average glucose level for the intraoperative period was significantly reduced in the aggressive insulin therapy (AIT) group as compared to the standard insulin therapy (SIT) group, however, the average glucose levels are above the range of 60-130 mg/dL (page 1013, left column; Fig. 1).

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating a critically ill patient or a CIPNP patient using various blood glucose regulators. The specification indicates a critically ill patient or a CIPNP patient can be treated by controlling glucose metabolism during the critical illness by applying intensive treatment with a blood glucose regulator such as insulin (page 3). However, the specification has not demonstrated the treatment of CIPNP patients or critically ill patients using various blood glucose regulators other than insulin. Moreover, there are no working examples indicating the treating conditions such as the dosage, the time for treating patients with CIPNP or other critical illness using various blood glucose regulators which have different structures (e.g., sulfonylureas or thiazolidinediones) or different glucose-regulating mechanism (e.g., compounds that stimulating signal transduction mediated by an insulin receptor type tyrosine kinase) from insulin, nor demonstrating the effects of these blood glucose regulators. Since the specification fails to provide sufficient teachings on the treating conditions such as doses of various blood glucose regulators and the effects of these compounds for treating patients with CIPNP or other critical illness, nor has indicated how to extrapolate the dosage of insulin to

the doses of different glucose regulators for effective treatment, it is necessary to have additional guidance and to carry out further experimentation to assess the in vivo effects of these blood glucose regulators in the treatment of patients with CIPNP or other critical illness.

(6). Nature of the Invention

The scope of the claims encompasses a method of treating a critically ill patient or a CIPNP patient using various blood glucose regulators, but the specification has not demonstrated the treatment of CIPNP or other critical illness using various blood glucose regulators besides insulin. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed methods associated with the variants, the effect of various blood glucose regulators in the treatment is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of various blood glucose regulators in the treatment of patients with CIPNP or other critical illness.

In response, applicants indicate the present application provides far more than "cursory conclusions without data supporting the findings" as alleged by the Examiner, particularly the specification teaches that critical illness and CIPNP in a patient can be treated by strictly controlling glucose metabolism by utilizing a blood glucose regulator to maintain the patient's blood glucose levels within specifically defined ranges, which are based in vivo data from human patients demonstrating that strict control of blood glucose levels via administration of an exemplary blood glucose regulator, insulin, resulted in the successful treatment of both CIPNP patients and critically ill patients suffering a variety of diseases (Examples 1 and 2); and

numerous blood glucose regulators were widely available and prescribed to patients including sulfonylureas, thiazolidinediones or metformin, and the Examiner provides no evidence why on of ordinary skill in the art would not have been able to use such blood glucose regulators to maintain blood glucose levels within specifically defined ranges to treat critically ill and CIPNP patients (pages 7-8 of the response). The response has been fully considered, however, the argument is not found persuasive because the specification only demonstrates strict control of blood glucose levels via administration of a specific blood glucose regulator, insulin, resulted in the treatment of both CIPNP patients and critically ill patients suffering a variety of diseases (Examples 1 and 2), it has not demonstrated the treatment of CIPNP patients or critically ill patients using various blood glucose regulators which have different structures or different glucose-regulating mechanism from insulin, which are encompassed by the claims. Furthermore, there are no working examples indicating the effects of various blood glucose regulators other than insulin. Although numerous blood glucose regulators were widely available, some glucose regulators have very different structures (e.g., sulfonylureas or thiazolidinediones) from insulin, and some have different glucose-regulating mechanism (e.g., compounds that stimulating signal transduction mediated by an insulin receptor type tyrosine kinase), thus, the treating conditions such as the dose and the time for these compounds in the treatment have to be taught or obtained from further experimentation. Since the specification has not provided sufficient teachings on the treating conditions for these various blood glucose regulators, nor has indicated how to extrapolate the dosage of insulin to the doses of different glucose regulators for effective treatment, it is necessary to have further experimentation to search for the proper doses in the

treatment and to assess the effects of various blood glucose regulators, thus the full scope of the claims is not enabled as indicated in the section above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 4-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-14 are indefinite because the claims lack an essential step in the method of treating a patient suffering from CIPNP. The omitted step is the outcome of the treatment, to treat said CIPNP is not the endpoint of the treatment since the claim does not indicate the effect of administering a glucose regulator. Claims 5-14 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicate the claim has been amended to include the steps. The response has been considered, however, the argument is not fully persuasive because the term "to treat CIPNP" does not indicate the effect of administering a glucose regulator in the treatment, e.g., reducing the incidence of CIPNP and lengthening the time free of CIPNP in patients (see page 17, lines 24-31).

Conclusions

9. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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Chih-Min Kam, Ph. D. CMK
Patent Examiner

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May 21, 2004